IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bell *et al.* Confirmation No.: 4773

Appl. No. 09/664,444 Art Unit: 1645

Filed: September 18, 2000 Examiner: R. Zeman

For: **ONCOLYTIC VIRUS** Atty. Docket: 18003

Cust. No. 31976

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This Reply Brief is in response to the Examiner's Answer dated November 20, 2009. Since this Reply Brief is being filed within two months of the date of the Examiner's Answer, this Reply Brief is timely filed.

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I. STATUS OF CLAIMS

Claims 1, 6-13, 19, 24-37, 64-77 and 79-80 have been rejected and are under appeal.

Claim 78 is objected to as being dependent on a rejected claim.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The two grounds of rejection for review by the Board is whether:

(i) claims 27-31 and 73-77 are unpatentable under 35 U.S.C. § 112, first paragraph, for failing to meet the enablement requirements without a biological deposit; and

(ii) claims 1, 6-13, 19, 24-37, 64-77 and 79-80 are unpatentable under 35 U.S.C. § 112, first paragraph, for failing to meet the enablement requirement.

III. ARGUMENT

Applicants present the following in response to the Examiner's Answer. Applicants believe that the Examiner's Answer does not rebut the arguments put forth in Applicants' Appeal Brief of June 15, 2009. However, the following is provided to address certain statements made in the Examiner's Answer. Therefore, Applicants request that the Board consider the following in addition to the arguments presented in the Appeal Brief.

A. Melanoma Cells Versus Hematopoietic Tumor Cells

In various sections of the Examiner's Answer, the Examiner indicates that the claims relate to melanoma cells. For Example, see page 5, last three lines; page 7, first and second paragraph; and page 10, line 12. In fact when referring to the pending claims, the Examiner states "[s]aid melanoma tumor cells can optionally be leukemia cells or myeloma". (page 5, last line.) On the contrary, the independent claims recite that the tumor cell is a hematopoietic tumor cell, and a melanoma tumor cell is not a hematopoietic tumor cell. In addition, leukemia cells and myeloma cells are not types of melanoma cells. Therefore, the Examiner's remarks related to the claimed invention being drawn to melanoma cells are not correct.

B. The Claims Refer to the Virus Being a VSV

In various sections of the Examiner's Answer, the Examiner indicates that the claims relate to viruses other than VSV. This is clearly not correct.

As an example, the Examiner states that "the specification is silent on the [sic] what viruses other than VSV would induce the claimed anti-tumor effect." (Examiner's Answer, page 6, underlining added.) Also, see page 7, first line, of the Examiner's Answer. Clearly, the specification does not have to enable the use of viruses that are not within the scope of the claimed invention.

C. Specification Provides Results for Various Hematopoietic Tumor Cell Lines

> The bottom of page 6 of the Examiner's Answer states
>
> while the specification has demonstrated only two leukemia cell lines (MD7E [sic] and L1210), a couple of AML cell lines . . ., one CML cell line . . . and a T-cell leukemia . . . that are susceptible to VSV infection. VSV was shown to reduce the viability of only the AML, CML and T-cell leukemia cell lines.

This statement is not correct and alleges that VSV was not shown to reduce the viability of the two leukemia cell lines (M07E and L1210). However, this is not the case. The specification states "two leukemia cell lines (M07E and L1210) were also tested and found to be susceptible to VSV infection as evidenced by cytopathic effect, virus growth and loss of cell viability" (page 19, lines 29-31) and "[t]wo leukemia cell lines (M07E and L1210; Table 1) were killed following an overnight infection and produced large amounts of virus." (page 30, lines 11-12.) Therefore, it is not possible to conclude that VSV did not reduce the viability of these two leukemia cell lines.

D. Specification Provides Guidance on Methods of Administration

At the bottom of page 7 of the Examiner's Answer, the Examiner states "the specification is equally silent on how said viruses are to be administered to said subject." Applicants respectfully disagree. Not only do the Examples in the specification provide examples of various routes of administration for the virus (*e.g.*, intravenous, intranasal or intratumoral), pending claim 34 and original claims 32 and 34 describe routes for administering the virus to a subject. Therefore, the specification is not "silent on how said viruses are to be administered to said subject".

E. The Anti-tumor Effect of VSV Mutants Is Predictable

When referring to Example 25 of the specification, the Examiner states "said example only utilizes two of the five VSV mutants disclosed in the instant specification suggesting that the anti-tumor effect of the disclosed VSV mutants is unpredictable." (Examiner's Answer,

page 10.) Testing only two of five mutants does not suggest that the anti-tumor effect of other VSV mutants is unpredictable.

F. Kelland Teaches That Xenograft Model is a Good Predictor of Clinical Activity

Applicants' Appeal Brief provided the following quote from Kelland (Eur. J. Cancer. 2004, 40(6):827-836),

> one may reasonably conclude that, at least for cytotoxic cancer drugs, the human tumour xenograft model, is a good predictor of clinical activity.

(Kelland, page 831, first column, quoted on page 24 of the Appeal Brief.) The Examiner alleges that this quote "is taken out of context as Kelland et al. was summarizing the correlation between xenografts models and hollow fiber based models." (Examiner's Answer, pages 21 and 24.) Applicants respectfully disagree. For the convenience of the Board, Applicants provide below the full paragraph containing the quoted passage. For convenience, the previously quoted passage is italicized

> Overall, taking all of the above into consideration, *one may reasonably conclude that, at least for cytotoxic cancer drugs, the human tumour xenograft model, is a good predictor of clinical activity.* Therefore, it seems reasonable and valuable, to continue the testing of new cytotoxics using xenografts. This is especially the case when used in combination with sound pharmaceutical and pharmacological principles (see below). Notably, some regulatory authorities (e.g. the European Medicines Evaluation Agency (EMEA) in its guidance notes on the preclinical evaluation of anticancer medicinal products, encourage the use of xenograft studies (http:// www.eudra.org/emea.html).

(bridging pages 831-832, emphasis added.) While the paragraph before this quoted paragraph does refer to the comparison of hollow fibre assays to xenograft models, it does not change the meaning of the paragraph quoted above. In fact, the quoted paragraph is the last paragraph of a section of Kelland that discusses the ability of studies in xenograft models to predict or correspond to clinical activity in human patients.

Additionally, the Examiner states "Kelland discloses that the xenograft model is an effective screen for candidates for Phase I clinical trials and contrary to Appellant's assertion does not constitute a predictor of *in vivo* efficacy." (Examiner's Answer, page 24.) To the contrary, the fact that those skilled in the art believe that a model is an effective screen for

candidates for Phase I clinical trials indicates that they believe that the model reasonably correlates with clinical activity.

G. Pecora *et al.* is Not Limited to Solid Tumors

The Examiner stated "Pecora et al. is limited to solid tumors". (Examiner's Answer, page 22.) However, Table 2 of Pecora *et al.* lists the various tumor types for the treated patients. Two of these patients are listed as having lymphoma, which is not a solid tumor. To be fair, Pecora *et al.* is silent as to whether or not either of these two patients were in the group that responded to virus treatment.

However, this is not really pertinent to the reason Applicants cite Pecora *et al.* The Examiner had previously presented various references that allegedly showed that *in vitro* assays and xenograft models are not predictive of clinical activity for anti-tumor agents, but none of those references discussed oncolytic viruses as anti-tumor agents. Applicants cited Pecora *et al.* (and McCormick (U.S. Patent No. 5,677,178)) to show that oncolytic viruses that were previously tested *in vitro* and in xenograft models did show clinical activity in patients.

H. Bibby Does Not Disclose That Leukemias Are Harder to Treat

The Examiner states that "as pointed out by the Appellant, . . . Bibby discloses that leukemias are difficult to treat." (Examiner's Answer, page 25.) Applicants respectfully disagree.

Bibby discloses no such thing. If anything, Bibby discloses that leukemias were easier to treat than solid tumors with the agents they tested, not that leukemias are difficult to treat. For example, Bibby states:

> In the past, murine tumour systems were used for drug screening with mouse leukaemias being utilised as prescreens [1]. These grew very rapidly, had a high growth fraction and proved to be sensitive to a number of agents that were subsequently shown to have more activity against leukaemias and lymphomas than against solid carcinomas and sarcomas . . .

(page 852.)

I. Use of VSV as Claimed is Enabled

Applicants' Appeal Brief of June 15, 2009 pointed to statements made by the Examiner during prosecution of Application No. 11/685,483[1] ('483 application), which claims priority to the present application. The Examiner had stated in the '483 application that "the use of VSV as a cancer treatment is well known in the art yielding predictable results". (April 10, 2008, Office Action, page 21, for U.S. Patent Application No. 11/685,483.)

In the Examiner's Answer, the Examiner responded that this statement was made in a rejection under 35 U.S.C. § 103(a) that "dealt with the *in vitro* treatment of tumor cells . . ." (Examiner's Answer, page 27.) On the contrary, as the Examiner mentions in the Examiner's Answer claims 1, 10-12 and 18-19 were included in this rejection under 35 U.S.C. § 103(a) of the '483 application. These claims are reproduced below. Claims 10-12 and 18-19 clearly referred to *in vivo* and not *in vitro* administration, so the Examiner's allegation that his statement that "VSV as a cancer treatment is well known in the art yielding predictable results" was only referring to *in vitro* "treatment" is not correct. Otherwise, the claims to *in vivo* tumor cells, especially claim 11 to the tumor cells being in a human subject, would not have been included in the rejection under 35 U.S.C. § 103(a) of the '483 application.

Claims of U.S. Patent Application No. 11/685,483[2]

1. A method of reducing the viability of a tumor cell, comprising administering to the tumor cell a vesicular stomatitis virus,
wherein said tumor cell is a carcinoma,
wherein the virus is contained in a cell infected with the virus, and
wherein the administering comprises administering the virus-infected cell.

10. The method of claim 1, wherein the tumor cell is in a mammalian subject.

11. The method of claim 10, wherein the mammalian subject is a human.

12. The method of claim 10, wherein the administering comprises administering the virus-infected cell to the subject-intratumorally.

18. The method of claim 10, wherein the administering comprises administering the virus-infected cell to the subject intravenously.

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[1] The Examiner's Answer incorrectly refers to this application as Application No. 11/385,483.
[2] pending as the April 10, 2008, Office Action

19. The method of claim 10, wherein the administering comprises administering the virus-infected cell to the subject intraperitoneally.

Summary

As discussed above, Sections A though I above are provided only to correct and/or specifically address selected statements presented in the Examiner's Answer. Applicants believe their previously filed Appeal Brief, alone, rebuts all of the Examiner's outstanding rejections.

This Reply Brief addresses statements related to whether xenograft models reasonably correlate with therapeutic results in human patients. However as discussed in detail in the Appeal Brief, the claims do not require therapeutic benefit. It is not essential to the enablement requirement whether this claimed invention produces a therapeutic benefit or cure.

The Examiner has not presented any reasons or evidence that show or suggest that one skilled in the art cannot reduce the viability of a hematopoietic tumor cell *in vitro* or *in vivo*, even in an immunocompetent animal, using the claimed methods. In other words, the claims are enabled as long as one skilled in the art at the time of filing, using the teachings of Applicants' specification, could reduce the viability of a hematopoietic tumor cell commensurate with the scope of the claimed methods. There has been no adequate reasoning or evidence presented to the contrary. Therefore, a *prima facie* case for lack of enablement has not been made.

In view of the above and arguments presented in the Appeal Brief, Applicants respectfully request withdrawal of the rejection of (i) claims 27-31 and 73-77 under 35 U.S.C. § 112, first paragraph, for failing to meet the enablement requirement and (ii) claims 1, 6-13, 19, 24-37, 64-77 and 79-80 under 35 U.S.C. § 112, first paragraph, for failing to meet the enablement requirement.

IV. CONCLUSION

Reversal of all rejections is respectfully requested.

No fee is believed necessary in connection with the filing of this Reply Brief. If any fee is required, the Commissioner is hereby authorized to charge the amount of such fee to Deposit Account No. 50-1677.

Respectfully submitted,

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